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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,213	06/22/2000	Matheus Hubertus Maria Noteborn	LEBV.004.01U	6984

24247 7590 08/29/2002

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	17

DATE MAILED: 08/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Acti n Summary	Application No.	Applicant(s)	
	09/403,213	NOTEBORN ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

– The MAILING DATE of this communication appears on the c ver sheet with the correspondence address –

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-16 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-16 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 October 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-2, 4-16 and 22-27 are pending examination.

Applicants' traversal, addition of claims 22-27, cancellation of claims 3 and 17-21, and the amendment to claims 1-2 and 4-16 in paper no. 15 is acknowledged and considered.

The amendment encompassing the cross reference in the specification in paper no. 15 has been entered.

Noncompliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): page 10 list nucleotide sequences, but do not list a SEQ ID NO for each nucleotide sequence.

NOTE: In response to this office action, applicants are required to comply with sequence rules for all nucleotide sequences listed in the specification or the response will be considered non-responsive.

Priority

Note: This instant application does not enjoy priority to pending application 09/740,676 filed on 12/18/00 because '676 was filed 6 months **after** the instant application.

Therefore, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application (which is called a continuation) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional

application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht,* 168 USPQ 293 (CCPA 1971). The parent application, 08/842,161, filed 6/7/95 coupled with the state of the prior art prior to June 7, 1995, does not adequately the availability of: A gene delivery vehicle comprising a modified translation initiation site directly upstream of the ATG initiation codon, wherein said translation initiation site comprises the nucleic acid sequence GCCAAC; A host cell comprising gene delivery vehicle, which is a helper cell or packaging cell; A method of inducing apoptosis in a mammalian cell by administering a gene deliver vehicle further comprising administering chemotherapy, and thus, the parent application 08/842,161, does not contain an adequate support of description of the claimed material and/or methods which are essential for the practice of the claimed invention, therefore priority for the claims readable of the specifically cited can only be granted to the filing date of the instant application, June 22, 2000, which claims priority to a national application with a foreign priority dated 4/15/97.

Drawings

NOTE: In the next response, please submit a response to the PTO 498 because a PTO 498 was filed with the non-final rejection dated 12/6/01 and the applicants have not submitted proposed corrections to the drawings. If the reply to the Non-Final Rejection does not have a response to the 498, the response will be considered non-responsive. See 37 CFR 1.85(a).

Claim Objections

Claim 4 is objected to because of the following informalities: Claim 4 recites an improper grammatical phrase "nucleic acid encoding chicken anemia virus protein VP2". Suggest inserting the term "a" before the word "chicken". Appropriate correction is required.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The rejection under 112 first paragraph, written description, is moot in view of the amendment to the claims. See page 5.

However, a new rejection under 112 first paragraph, written description follows because of the amendment to claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-16, and 22-27 as best understood, are readable on a genus of a nucleic acid molecule encoding apoptin protein, wherein the genus of the nucleic acid molecule comprising apoptin protein is not claimed in a specific biochemical or molecular structure that could be

envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates using a nucleic acid molecule encoding apoptin-like activity protein in production of a gene delivery vehicle. The specification coupled with the state of the art provides sufficient description of the chicken anemia virus protein VP3; see Noteborn et al., WO 95/03414. Furthermore, the as-filed specification provides sufficient description of one species of apoptin protein and its C-terminal 50 amino acids that contain apoptotic activity (pages 1 and 19). The as-filed specification does not provide an adequate written description of a representative number of species of DNA molecule encoding apoptin protein other than the CAV VP3. It is apparent from the state of the prior art exemplified by Ngo *et al.* (The Protein Folding Problem and Tertiary Structure Prediction, Birkhauser Boston, 1994, pp. 491-494) that the description of the primary sequence of amino acid residues in which the positions of the amino acid residues are particularly arranged is essential for the biological function of the protein encoded by the sequence. This essential element that is required for an adequate description of a representative number of species as embraced by the claimed genus of apoptin encoded nucleic acid sequences is neither described sufficiently in the specification nor conventional in the prior art. The description of one polynucleotide sequence encoding an apoptin protein (VP3) without providing the essential and specific arrangement of the amino acid residues positioned in the sequence does not lend evidentiary support for a skilled artisan to have recognized that applicant was in possession of the genus of apoptin encoded nucleic acid sequences as claimed,

particularly since the essential element of the coding sequence of a generic apoptin is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine the primary sequence of the representative number of species of apoptin encoded genes or nucleic acids on the basis of the only disclosure of the chicken anemia virus protein VP3.

Furthermore, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a nucleic acid molecule encoding an apoptin protein as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of a genus of a nucleic acid molecule encoding an apoptin protein that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a nucleic acid molecule encoding an apoptin protein. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of a nucleic acid molecule encoding an apoptin protein that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a nucleic acid molecule encoding an apoptin protein that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicants' traversal is not found persuasive because it is not applicable to the rejection under 112 written description set forth above.

Claims 1-2, 4-16, and 22-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A gene delivery vector comprising a nucleic acid sequence encoding the chicken anemia virus protein VP3 or the C-terminal 50 amino acids of the VP3 protein; 2) A gene delivery vector comprising a nucleic acid sequence encoding the chicken anemia virus VP2; 3) The gene delivery vector of 1, further comprising a nucleic acid sequence encoding the chicken anemia virus VP2 protein; 4) The gene delivery vector of 3, further comprising at least one target molecule, wherein the target molecule is reactive with a tumor cell

surface receptor; 5) A host cell comprising the gene delivery vector of 4; 6) A method for inducing apoptosis in a mammalian tumor by directly administering to the tumor the gene delivery vector of 1, 7) The method of 6 further comprising using chemotherapy; and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a nucleic acid molecule encoding an apoptin protein), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g.. function in a gene delivery vehicle for use in a method of inducing apoptosis in tumor cells.

The field of the invention lies in a gene delivery carrier used in a method of cancer gene therapy or in an in vitro method of diagnosis cancerous cells.

Furthermore, and with respect to claims 22-26 directed to any gene delivery vehicle useful for gene therapy and directed to any therapeutic treatment of a mammal; the state of the

art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target

tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, at the time the application was filed gene therapy was considered unpredictable.

The specification provides working examples: The construction of recombinant vector comprising a nucleic acid encoding the chicken VP3 protein and using several packaging and helper cell lines (pages 8-16). On page 17, the disclosure examined whether the construct would induce apoptosis in isolated cell cultures comprising human transformed (page, 17, lines 19-20) and/or malignant cell lines (line 23). The construct exhibited apoptosis in different mammalian tumorigenic and transformed cell lines (Fig 4). On page 18 displays the construct did not induce apoptosis in an isolated culture of normal non-transformed human cells. On page 19 the disclosure examined the effect of incorporating a nucleic acid sequence in front of the ATG-initiation codon for the chicken VP3 protein. The result is 5 times more VP3 expression compared to the original direct upstream sequence. On page 20, the disclosure co-expresses two vectors (one vector comprising the chicken VP2 protein and the other vector comprising the chicken VP 3 protein) in an isolated culture of Saos-2 cells. The results in Figure 5 show that VP2 enhances the apoptosis. The disclosure produces a retrovirus vector expressing VP3 and showed that the vector can induce apoptosis in an isolated culture of human tumor cells (pages 21-22). On page 23, the disclosure prophetically contemplates how a diagnostic assay comprising rAD-VP3 would function. On pages 23-26, the specification determined toxicity in experimental rats by intravenously, intra-peritoneally, or subcutaneously injection. The results showed that the expression of VP3 has not toxic effect in vivo. On pages 26-29, the disclosure

used nude mice and injected subcutaneously into the nude mice tumorigenic cells and after the tumors developed, the specification intra-tumorally injected rAd-VP3 and control rAD-con1 vectors into the tumors. The results showed that the tumors injected with rAD-VP3 vector were reduce in sized compared to the tumors injected with the control vector.

The disclosure provides sufficient guidance for how these experiments reasonably correlate to an in vivo method of gene therapy for treating tumor cells in any mammal comprising intra-tumoral administration to said mammal with a recombinant replicant defective vector. In addition, the as-filed specification is enabled for the treatment listed above further comprising using chemotherapy. However, these experiments do not reasonably correlate to any other in vivo method of gene therapy for treating any other type of cancer cell using intravenous, intraperitoneal, dermal, nasal, buccal, rectal, vaginal or topical administration of recombinant vector comprising a nucleic acid sequence encoding VP2 and VP3.

In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. Nonetheless, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious

contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).

Vile further discusses:

A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

In view of the concerns set forth by the state of the art, the as-filed specification does not reasonably address the concerns put forth by the state of the art for cancer gene therapy.

Furthermore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration would result in a therapeutic response using the recombinant replicant defective vector comprising nucleic acid sequences encoding the chicken VP3 and VP2 proteins. The specification displays that VP3 reduces tumor size in nude mice by direct administration of the replicant defective adenovirus.

The state of the art for the route of administration for gene therapy as exemplified by Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). In view of the state of the art, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to any other route of administration to generate a therapeutic response in any subject with cancer.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed virus or replicant viruses generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy methods as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In addition with respect to the claimed apoptin protein (e.g. claim 1) and in further view of reasons set forth above. The as-filed specification provides sufficient guidance for the CAV VP3 protein or the C-terminal from the VP3 protein described in the specification, however, it is not apparent to one skilled in the art how to reasonably extrapolate from the VP3 protein the genus of an apoptin protein [*e.g.* the as-filed specification does not describe any SEQ ID NOs encoding the VP3 protein]. Furthermore, because of the lack of guidance, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (*e.g.*, see Chiu et al., *Folding and Design*, Vol. 3, pp.

223-228, 1998), it would require an undue amount of extended experimentation to determine which apoptin protein other than the VP3 described in the specification would function for an apoptotic activity. With the reasons set forth above it would require an undue experimentation to identify other nucleic acid molecules having apoptin protein other than the VP3 set forth in the as-filed specification.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable for 1-7, listed above. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable after the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery carrier cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicants' traversal is found partially persuasive for 1-7 listed above. However, the applicants' traversal is not found persuasive to the rejection under 112 enablement.

The rejection under 112 second paragraph, are moot in view of the amendment to the claims. See pages 5-6. However, in view of the amendment, new rejections under 112 second paragraph follow:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 14, 22-23 and 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The statement in claim 14, "... **a** gene delivery vehicle according to claim 13" is indefinite because it does not point out which composition **a** gene delivery vehicle is referring to in the claim. The claim that 14 is dependent on refers to one gene delivery vehicle and claim 14 refers to several gene delivery vehicles. The dependent claim should state "A host cell comprising **the** gene delivery vehicle according to claim 13".

To the extent that the applicants traversal is applicable to the rejections under 112 second, the traversal is not found persuasive for because it is not applicable to the rejection.

Claim 23-24 and 26-27 recite the limitation "a mammalian cell according to claim 22". There is insufficient antecedent basis for this limitation in the claim. Claim 22 or claim 25 is directed to a method.

To the extent that the applicants traversal is applicable to the rejections under 112 second, the traversal is not found persuasive for because it is not applicable to the rejection.

Note on priority: This instant application does not enjoy priority to pending application 09/740,676 filed on 12/18/00 because '676 was filed 6 months **after** the instant application.

A gene delivery vehicle comprising chicken anemia virus protein 2 (VP2) and/or **chicken anemia virus protein 3 (VP3)** only enjoys priority 7/19/94 because PCT/NL/00163 filed on 9/11/91 does not provide support under 112 first paragraph for the tumor inducing property of VP2 or VP3.

Claim 1 only enjoys priority to 4/15/97 and does not enjoy priority to any other application because support under 112 first paragraph for an **apoptin protein** was not provided by any of the other applications.

Claims 22, 23, and 25-26: A method for inducing apoptosis in tumor using a gene delivery vehicle comprising chicken anemia virus protein 2 (VP2) and/or chicken anemia virus protein 3 (VP3) only enjoys priority 7/19/94 because PCT/NL/00163 filed on 9/11/91 does not provide support under 112 first paragraph for the apoptosis property of VP2 or VP3.

Claims 24 and 27: A method for inducing apoptosis in tumor using a gene delivery vehicle comprising chicken anemia virus protein 2 (VP2) and/or chicken anemia virus protein 3 (VP3) and further comprising chemotherapy only enjoys priority 4/15/97 because PCT/NL/00163 filed on 9/11/91 does not provide support under 112 first paragraph for a method for inducing apoptosis in tumor using a gene delivery vehicle comprising chicken anemia virus protein 2 (VP2) and/or chicken anemia virus protein 3 (VP3) further comprising chemotherapy.

Claim Rejections - 35 USC § 102

The rejection under 102(b) and 102(e) are moot in view of the amendment to claim priority. See pages 6-7.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 4, 6, 8, 12, 13, 14, 22, 23, 25, and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Noteborn et al. (US Patent No. 6,071,520, effective filing date 7/19/1994). Noteborn teaches producing compositions comprising VP1+VP2 or VP1+VP2+VP3 or separately (column 3, line 65 – column 4, line 25). Furthermore, Noteborn teaches that CAV proteins VP2 and/or VP3 can be used in treatments for reducing (human) tumor formation. (column 5, lines 30-51). The VP3 protein can be expressed in tumors by means of DNA transfection by infecting the cells with retroviral vectors that contain a coding sequence for VP3.

To the extent that applicants' traversal (See page 6-7) is applicable to the new rejection under 102(e), the traversal is not found persuasive because the applicants have not provided the proper evidence to overcome a 102(e). See MPEP 706.02(b) for how to overcome a 102(e) rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noteborn et al. (US Patent No. 6,071,520, effective filing date 7/19/1994) taken with Donahoe et al. (US Patent No. 5,661,126, effective filing date 1/23/93). Noteborn teaches that CAV proteins VP2 and/or VP3 can be used in treatments for reducing (human) tumor formation. The VP3 protein can be expressed in tumors by means of DNA transfection by infecting the cells with retroviral vectors that contain a coding sequence for VP3 (column 5, lines 31-67. However, Noteborn does not specifically teach a method of inducing tumor cell death in a mammal by directly administering a vector to said tumor further comprising chemotherapy.

However, at the time the invention was made, chemotherapy in combination with gene therapy was well known in the art for treating tumors in a mammal as taught by Donahoe.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Noteborn with Donahoe, namely to use chemotherapy in a method of inducing tumor cell death in a mammal by directly administering a vector to said tumor. One of ordinary skill in the art would have been motivated to further employ chemotherapy for inducing tumor cell death in a mammalian subject in addition to directly administering the vector set forth above into said tumor.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

To the extent that the applicants' traversal is applicable to the rejections under 103(a) the traversal is not found persuasive for the reasons set forth above under the 102(e) rejection and because it is not applicable to the rejection.

Double Patenting

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-23 and 25-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,981,502. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims from '502 are directed to a method of effecting apoptosis in tumor cells, said method comprising: providing to said tumor cells a nucleotide sequence derived from a chicken anemia virus genome that codes for a protein thereof that induces apoptosis, wherein the said protein is VP2 or VP3. In addition, one skilled in the art understands that naked DNA is considered a gene delivery vehicle.

To the extent that the applicants' traversal is applicable to the rejections under double patenting, the traversal is not found persuasive for because it is not applicable to the rejection.

Claims 1, 4, 6, 8, and 22-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23-29, 31-33 and, 37-41 of U.S. Patent No. 6,162,461. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims from '461 are directed to a method of inducing apoptosis in tumor cell, said method comprising: transfecting said cell with an expression vector encoding one or both of a polypeptide depicted in Fig 3. or Fig 2.

To the extent that the applicants' traversal is applicable to the rejections under double patenting, the traversal is not found persuasive for because it is not applicable to the rejection.

Claims 22, 23, 25, and 26 are directed to an invention not patentably distinct from claims 23-29, 31-35, and 37-41 of commonly assigned patent 6,162,461. Specifically, the claims from

'461 are directed to a method of inducing apoptosis in tumor cell, said method comprising: transfecting said cell with an expression vector encoding one or both of a polypeptide depicted in Fig 3. or Fig 2.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned inventions, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Claims 22, 23, 25, and 26 are directed to an invention not patentably distinct from claims 1-7 of commonly assigned patent 6,162,461. Specifically, the claims from '461 are directed to a method of effecting apoptosis in tumor cells, said method comprising: providing to said tumor cells a nucleotide sequence derived from a chicken anemia virus genome that codes for a protein

thereof that induces apoptosis, wherein the said protein is VP2 or VP3. In addition, one skilled in the art understands that naked DNA is considered a gene delivery vehicle.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned inventions, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
8/26/02

DAVE T. NGUYEN
PRIMARY EXAMINER